REMARKS

Applicants respectfully request entry of the foregoing revised claim set into the application. As the present amendment further amends the claims and adds new claims, in order to expedite prosecution, applicants are filing this amendment together with a Request for Continued Examination.

In order to avoid confusion about marking amendments newly submitted in relation to those previously submitted (but not yet entered), applicants have replaced claims 1-38 with a parallel set of new claims 39-76. Claim 1 (now presented as new claim 39) has been amended further by adding the phrase "wherein said at least one antibody is administered in an amount effective for inactivating or depleting B-cells in said subject", support for which is found on page 18, lines 24-26 and in Example 1 of the present specification. Claim 1 (now claim 39) is further amended to clarify that the anti-CD22 antibody is one which targets the A, B, D, or E epitope of CD22, support for which is found in the paragraph bridging pages 14 and 15. Claim 6 (now claim 44) is amended to be consistent with the amendments to claim 1 (now claim 39). Claim 46 has been amended to include B-cells in the list of targets of a second therapeutic step, support for which is found in the paragraph bridging pages 16 and 17. Claims 77-79 are added as dependent claims to cover preferred embodiments of claim 39, support for which is found in the paragraph bridging pages 16 and 17. Lastly, Claim 80 is added to cover preferred hybrid antibodies, support for which is found at page 3, lines 15-25. Claims 39-80 will be pending upon entry of this amendment.

Applicants appreciate the Advisory Action's indication that the previously submitted amendments will be entered upon filing of a Notice of Appeal and that the previous response has overcome the deposit-related rejection. These amendments have been incorporated into the newly added claims above.

The only remaining issue in this application is two obviousness rejections under 35 U.S.C. 103(a) of the claims based upon a combination of references: Aruffo, Meyer, Anderson, Tedder, Merck Manual, and Leung. Reconsideration of the rejections is respectfully requested.

Applicants first wish to stress that, even if Tedder and Aruffo were combined, the presently claimed invention would not result because Tedder and Aruffo both teach antibodies that are outside the scope of the presently claimed invention. As for the other references, they would not be utilized in autoimmune therapy absent a suggestion from the prior art to employ them for that purpose. As explained below, Tedder and Aruffo deal with specific types of antibodies that do not give rise to any suggestion to utilize an antibody from any of these other references. This is underscored in the accompanying Rule 132 Declaration of Dr. Hans Hansen, one of the co-inventors. As Dr. Hansen's Declaration firmly establishes, a person of ordinary skill in the art would ***not*** have been motivated by Aruffo's transient B-cell depletion, which is ***not linked*** to the sustained suppression of the host's antibody response (note that Fig. 3 of Aruffo shows that the suppression lasts beyond the time point at which B-cell levels had returned to normal) to turn to the other B-cell depleting antibodies of the remaining references.

ARUFFO RELATES TO A DIFFERENT MECHANISM. To begin with, Aruffo relates to a different mechanism for attacking autoimmune disease. Aruffo's invention relates to a blocking of the interaction between CD40 and its cognate ligand, gp39. The interaction between CD40 and gp39 "primes B cells to respond to subsequent stimulatory signals leading to B cell proliferation, differentiation and isotype switching" (Kiener *et al.*, *J. Immunol.* (1995)) and relates to "T cell-dependent B cell activation" (Foy *et al.*, *J. Exp. Med* (1993)). See also, product information for anti-mouse CD154 ("gp39 is expressed transiently by activated T cells...gp39 interaction with CD40 transduces signals for T-dependent B-cell activation" -- http://www.ebioscience.com/ebioscience/specs/antibody_16/16-1541. ***An antibody to CD19, CD20 or CD22 would not prevent interaction between CD40 and gp39, the function achieved by the Aruffo antibody, and thus a person of skill in the art would have no reason to substitute one of these antibodies for the Aruffo anti-CD40 antibody.***

The rejection cites portions of Aruffo that suggest that B cells are ***transiently*** depleted when the anti-CD40 antibody is administered. However, col. 9, lines 45-46 clearly states that "[r]ecovery of B cells to normal levels occurred within 2-3 weeks post-treatment." ***More importantly, Fig. 3 of Aruffo shows that a sustained suppression of the host's antibody***

response occurred beyond 3 weeks when B cells had returned to normal levels. As Dr. Hansen explains in his accompanying Declaration, a person of ordinary skill in the art would certainly not be motivated by these findings to utilize B-cell antibodies in the treatment of autoimmune disease. To the contrary, a person of ordinary skill would conclude in line with Aruffo's teaching that the B-cell depletion is an undesirable side effect that should be minimized rather than enhanced.

The result sought by Aruffo is a blocking of the interaction between CD40 and gp39 ("a key functional property for the desired anti-CD40 mAb was the capacity to completely block the interaction of CD40 and its ligand, gp39" – column 7, lines 21-24), leading to significant suppression of antibody response. To this end, Aruffo utilized various assay formats to select antibody candidates for further testing. From ***200*** initial candidates (column 7, lines 19-20), the field was limited to two for testing *in vivo* (column 8, lines 50-53). While both of these produced a transient reduction in peripheral B cell levels, ***only one of them, 2.220, significantly suppressed antibody response.*** The other candidate, 2.36 did not meet Aruffo's purpose. The clear message to be taken from Aruffo is that the ability to block interaction between CD40 and gp39 is a necessary, but not sufficient, basis for success in the ability to suppress antibody response and hence serve as a therapy in autoimmune diseases. It would not have been obvious that an antibody to CD19, CD20 or CD22 could be substituted for the anti-CD40 antibody of Aruffo, especially given that only one antibody in 200 was deemed by Aruffo to achieve the stated purpose of Aruffo's method.

ARUFFO'S CD40-BASED APPROACH IMPLICATES OTHER CELL TYPES THAT MAY CAUSE ADVERSE EVENTS. Yet another difference between the presently claimed invention and Aruffo is the fact anti-CD40 antibody targets an antigen also found on thrombocytes. See *Circ. Res.*, 2003 May 16;92(9):944-6, stating that "CD40 is constitutively expressed on platelets and provides a novel mechanism for platelet activation". Binding to other cell types like thrombocytes could cause adverse events. By contrast, tests utilizing CD20 and CD22 antibodies of the presently claimed invention have not revealed any thrombocyte-related adverse events. Similarly, Dr. Hansen states in his accompanying Rule 132 Declaration that he is not aware of any reports that CD19 is linked to thrombocytes, and

therefore, would not expect antibodies to CD19 to be associated with adverse thrombocyte-associated events. See *J Immunol.*, 1987 May 1;138(9):2793-9, stating that CD19 is "the broadest lineage specific surface marker for B cells: it is present on the surface of virtually all B lymphocytes, including early B progenitor cells. This underscores just one of the basic differences between the present approach and that of Aruffo.

TEDDER DOES NOT REMEDY ARUFFO'S DEFICIENCIES; TEDDER ONLY TEACHES USE OF CD22 ANTIBODIES THAT TARGET A DISTINCT EPITOPE FROM A, B, C, D, OR E OF CD22. In column 4, lines 32-35, Tedder clearly states that "[t]he present invention concerns a series of novel monoclonal antibodies (mAb), designated HB22, that specifically block cell adhesion to CD22." As shown in Table III of Tedder (col. 11), the antibodies of Tedder's invention do not bind to the A, B, C, D, or E epitopes of CD22. This is more clearly stated in col. 10, lines 64-67, where Tedder observes that "the region of CD22 that mediates ligand binding may be located in close proximity to a region overlapping epitopes B, C, and D."

TEDDER TEACHES DIRECTLY AWAY FROM USE OF CD22 ANTIBODIES AS PRESENTLY CLAIMED. In other words, Tedder's results show that Tedder's antibodies are distinct from antibodies of the prior art targeting the B, C, and D epitopes and that this is functionally a critical difference for Tedder's stated purpose because Tedder only utilizes antibodies that block cell adhesion to CD22. In sum, Tedder's entire patent is focused on identifying antibodies that target a new epitope of CD22 that is not the A, B, C, D, or E epitope, but rather a distinct epitope that is near B, C, and D (and may overlap them) that is responsible for blocking cell adhesion to CD22 (a function alleged by Tedder not to be obtained by the prior art antibodies). Thus, Dr. Hansen correctly concludes in his attached Rule 132 Declaration that Tedder would not motivate one of ordinary skill to select an antibody as presently claimed targeting the A, B, D, or E epitope of CD22 for use in autoimmune therapy.

EVEN IF ARUFFO AND TEDDER ARE COMBINED, THE PRESENTLY CLAIMED INVENTION DOES NOT RESULT. Aruffo's anti-CD40 antibodies are outside

the scope of the presently claimed invention. Tedder's anti-CD22 antibodies are also outside the scope of the presently claimed invention. Thus, even putting the two references together does not yield a method as presently claimed. More importantly, putting the two together does not yield a motivation for turning to any of the remaining references in the rejection teaching other antibodies (Anderson, Meyer, and Leung). Tedder teaches directly away from selecting an antibody of Leung. Tedder teaches one of ordinary skill to select only anti-CD22 antibodies that block adhesion based on a distinct epitope from A, B, C, D, and E. ***For this reason alone, it should be clear that the dependent claims in this application relating to the elected species are allowable.*** Furthermore, neither Tedder nor Aruffo provide any reason whatsoever for selecting an anti-CD20 or anti-CD19 antibody in a method of autoimmune therapy. The transient B-cell depletion noted in the rejection with Aruffo, which ends at 3 weeks, is ***not linked*** to the sustained suppression of the host's antibody response which occurred beyond 3 weeks (see Fig. 3 of Aruffo). As Dr. Hansen's Declaration firmly establishes, a person of ordinary skill in the art would ***not*** have been motivated by this transient B-cell depletion that is an unwanted side effect of anti-CD40 therapy and that is not linked to the sustained suppression of the host's antibody response to turn to other B-cell depleting antibodies.

ANDERSON FAILS TO REMEDY THE DEFICIENCIES OF ARUFFO AND TEDDER. Anderson is apparently cited only for teaching that CD20 antibodies are known for therapeutic use in treating cancer. The word "autoimmune" appears nowhwere in the Anderson reference. Absent a motivation to utilize B-cell depleting or inactivating antibodies in autoimmune disease, a person of ordinary skill in the art would not turn to Anderson for the purpose stated in the rejection.

MEYER LIKEWISE FAILS TO REMEDY THE CRITICAL DEFICIENCIES OF ARUFFO, TEDDER, AND ANDERSON. As with Aruffo, Tedder, and Anderson, Meyer does not contain one iota of motivation to select a B-cell-suppressing antibody for use in autoimmune therapy. The critical missing link in the rejection is that none of these references would have motivated a person of ordinary skill in the art to use an effective amount of an

antibody that inactivates or depletes B-cells for the purpose of autoimmune therapy as presently claimed.

THE MERCK MANUAL AND LEUNG ALSO FAIL TO REMEDY THE CRITICAL DEFICINCIES IDENTIFIED IN THE OTHER REFERENCES. The rejection acknowledges that the Merck Manual and Leung do not teach any motivation to select B-cell antibodies for autoimmune therapy. These references are only cited for specific teachings unrelated to the basic question of whether a person of ordinary skill in the art would have had any reason to attempt to use a B-cell-depleting or inactivating antibody in the first instance as a potential new autoimmune therapy.

In short, the cited combination of prior art fails to teach the elements of the presently claimed invention. Moreover, the prior art does not suggest that an advantageous method of autoimmune therapy would result that can avoid the potential adverse events associated with an antibody that binds to thrombocytes as with Aruffo.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Oct. 3, 2003 By _____

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